Synthesis of Deuterium Labeled (±)-2,5-Dimethoxyamphetamine (DMA), (±)-4-Bromo-2,5-dimethoxyamphetamine (DOB), and (±)-4-Methoxyamphetamine (PMA) as Internal Standards for Quantitative Analyses by GC-MS

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DMA, DOB and PMA are increasingly abused central nervous system stimulants with neurotoxic properties. In recent years, many controlled substance analogs (designer drugs) with a large variety of structures have reached the illegal market, making their identification difficult. Therefore, this work studies the synthesis of DOB-d_6, DMA-d_6 and PMA-d_3 as internal standards for use in gas chromatography-mass spectrometry (GC-MS) to identify controlled substances.

Keywords: (±)-2,5-Dimethoxyamphetamine; DMA; (±)-2,5-Dimethoxy-4-bromoamphetamine; DOB; (±)-4-Methoxyamphetamine; PMA; GC-MS.

INTRODUCTION

Unknown drugs are generally detected and identified by gas chromatography-mass spectrometry (GC-MS) because of the high sensitivity and ability of this method to separate organic compounds from complex mixtures. Based on electron impact (EI), this technique is commonly insufficient to discriminate between structurally closely related phenethylamine drug variants, because their mass spectra are commonly virtually identical to those of extremely poor molecular and fragment ions.[1-4] This fact strongly influences the capacity to detect novel amphetamine-controlled substance analogs.[5-6]

Some phenethylamines such as 4-bromo-2,5-dimethoxyphenethylamine (2C-B), 4-chloro-2,5-dimethoxyphenethylamine (2C-C), 4-iodo-2,5-dimethoxyphenethylamine (2C-I), 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2), 2,5-dimethoxy-4-*n*-propylthiophenethylamine (2C-T-7) and 5-methoxy-*N*,*N*-dimethyltryptamine; and some phenisopropylamines, as 2,5-dimethoxyamphetamine (DMA), 4-bromo-2,5-dimethoxyamphetamine (DOB) and 4-methoxyamphetamine (PMA) (Fig. 1) are increasingly abused

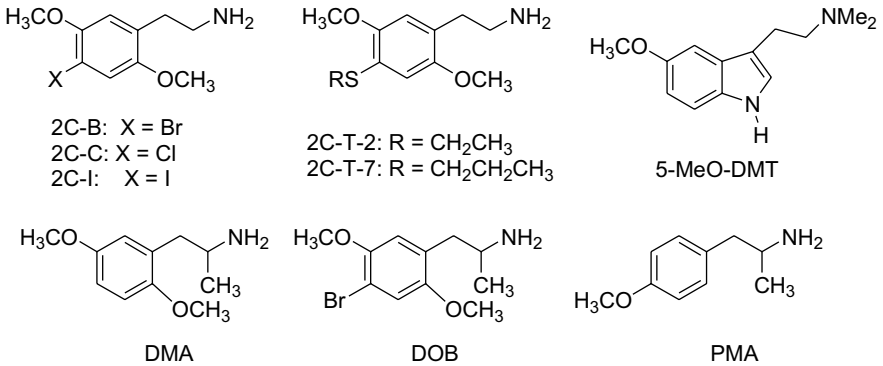

Fig. 1. The structures of 2C-B, 2C-C, 2C-I, 2C-T-2, 2C-T-7, 5-MeO-DMT, DMA, DOB and PMA.

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psychoactive drugs and have been well documented in the literature.[7-13] The widespread consumption of designer drugs has led to an increase in the number of reports on abuse and intoxication.

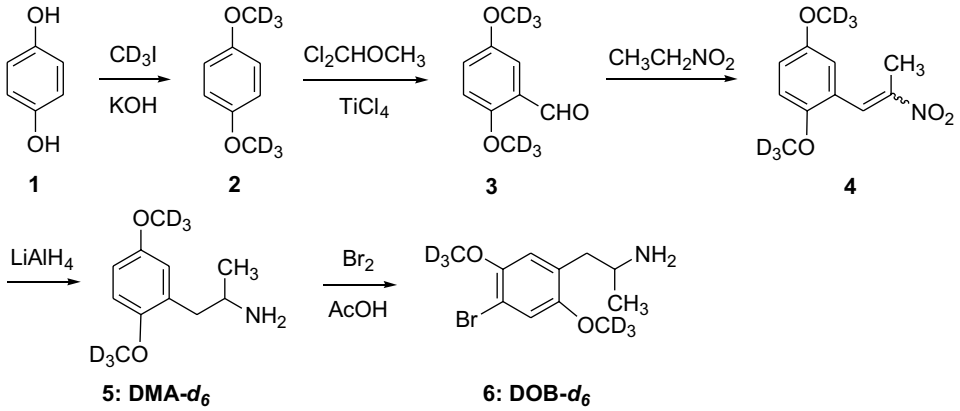
The abuse of psychoactive drugs from the phenethylamine and phenisopropylamine groups has become a very serious social problem in Taiwan during the last decade.[14-24] Amphetamine, its *N*-methyl homologues methylamphetamine, and ring-substituted analogues, 4-methylenedioxmethylamphetamine (MDMA), 3,4-methylenedioxyethylamphetamine (MDE), DOB, DMA and PMA are among those most widely taken by young people. Standard samples for controlled drug analysis in Taiwan are very difficult to obtain. This study describes synthetic routes to DOB-d_6, DMA-d_6 and PMA-d_3, and presents relevant characteristic analytical data. The synthetic approach described herein is potentially applicable to the synthesis of a wide variety of other amphetamine drugs. Meanwhile, applications of DOB-d_6, DMA-d_6 and PMA-d_3 as internal standards were also investigated in this work. According to the authors' knowledge, the literature includes no report on these compounds.

RESULTS AND DISCUSSION

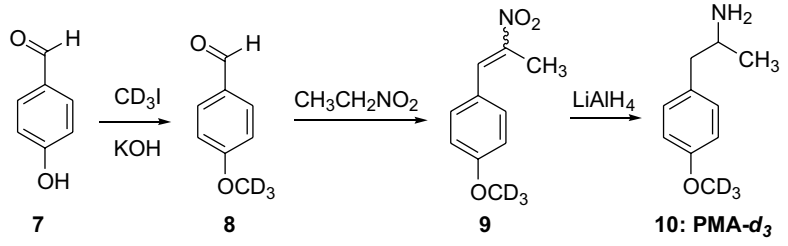
DOB, DMA and PMA are readily prepared using a number of synthetic routes.[25-37] However, the preparation of DOB-d_6, DMA-d_6 and PMA-d_3 has not been described previously. Scheme I is the general synthetic scheme for the preparation of the (±)-2,5-dimethoxyamphetamine-d_6 (**5**) and (±)-4-bromo-2,5-dimethoxyamphetamine hydrochloride-d_6, (**6**). 1,4-Dimethoxybenzene-d_6 (**2**) was prepared by reacting hydroquinone with methyl iodide-d_3.[38-40] Formylation with dichloromethyl methyl ether and $TiCl_4$ gave 2,5-dimethoxybenzaldehyde-d_6 (**3**),[41-46] and then condensation with nitroethane yielded 1,4-dimethoxy-2-(2-nitropropenyl)benzene-d_6 (**4**). Reduction with lithium aluminum hydride yielded (±)-2,5-dimethoxyamphetamine-d_6 (**5**), and bromination with bromine in acetic acid gave (±)-4-bromo-2,5-dimethoxyamphetamine hydrochloride-d_6, (**6**).[25]

Scheme II presents the preparation of 4-methoxyamphetamine-d_3 (**10**). *p*-Anisaldehyde-d_3 (**8**) was prepared by reacting 4-hydroxybenzaldehyde (**7**) with iodomethane-d_3.[38-40] The condensation of compound **8** with nitro-

Scheme I



Scheme II



ethane gave 1-(4-methoxyphenyl)-2-nitropropene-d_3 (**9**), and reduction with $LiAlH_4$ yielded (±)-4-methoxyamphetamine-d_3 (**10**).[25]

Both labeled and unlabeled compounds were derivatized by trifluoroacetic anhydride and analyzed by gas chromatography (GC). The retention times of GCs of three sets of labeled and unlabeled compounds vary very little (0.01 min), and the quantification by MS with the selected ion monitoring technique in order enhanced the performance of quantitative analysis (Table 1). The mass spectra of the compounds under investigation were obtained by conventional EI mass spectrometry (Figs. 2-7). The linearity of the method was determined by applying calibration standards at 0, 500, 1000 and 2000 ng of analyte. Linear regression of the calibration curves gave r^2 values of between 0.9968 and 1.000, with most values > 0.9900 (Table 2).

The EI mass spectrum of the (±)-*N*-[2-(2,5-dimeth-

Table 1. Retention times and ions monitored for GC/MS analysis

Compound	Retention time (min)	Ions monitored* (relative intensity, %)
DMA-d_6	5.19	**184**, 297 (93.2), 157 (92.5)
DMA	5.20	**178**, 291 (95.4), 151 (91.0)
DOB-d_6	6.12	**235**, 262 (86.8), 375 (60.8)
DOB	6.13	**229**, 256 (85.5), 369 (57.3)
PMA-d_3	4.60	**124**, 151 (40.3), 264 (11.32)
PMA	4.61	**121**, 148 (40.1), 261 (10.32)

*Quantification ions marked by bold.

Table 2. The linear regression of the calibration curves

Compound	Coefficient of correlation (r^2)	Regression line
DMA	0.9992	y = 0.0016x – 0.0214
DOB	0.9995	y = 0.0023x + 0.0473
PMA	0.9968	y = 0.0022x – 0.0406

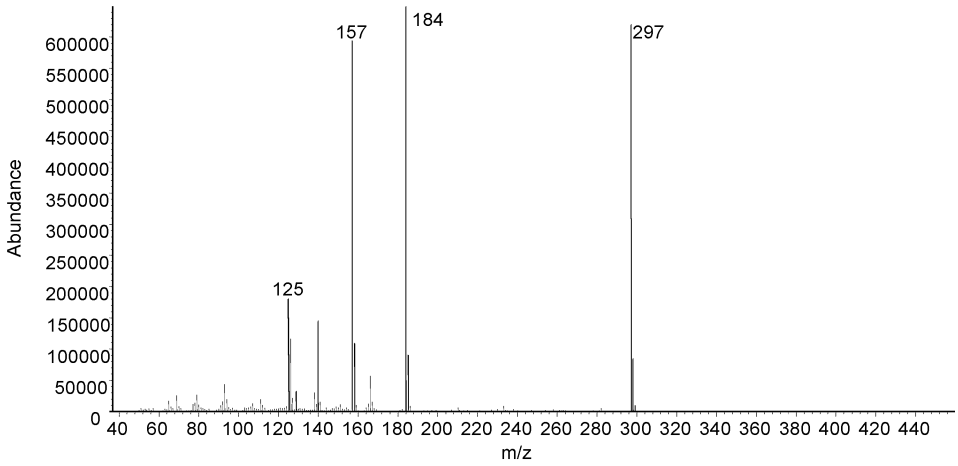


Fig. 2. The mass spectra of (±)-*N*-[2-(2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_6.

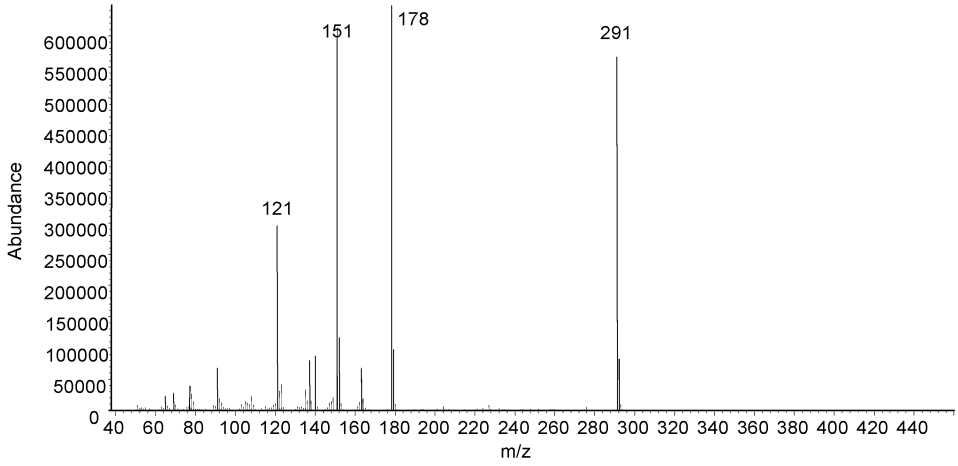


Fig. 3. The mass spectra of (±)-*N*-[2-(2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide.

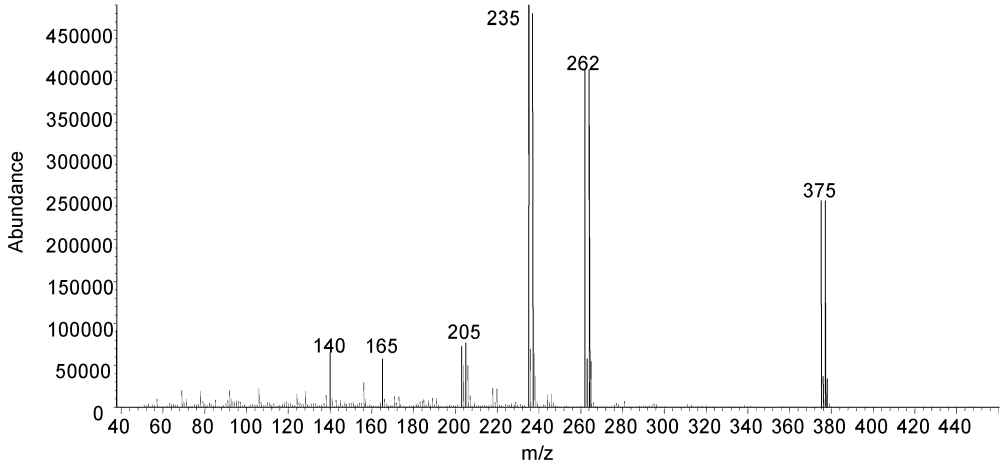


Fig. 4. The mass spectra of (±)-*N*-[2-(4-bromo-2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_6.

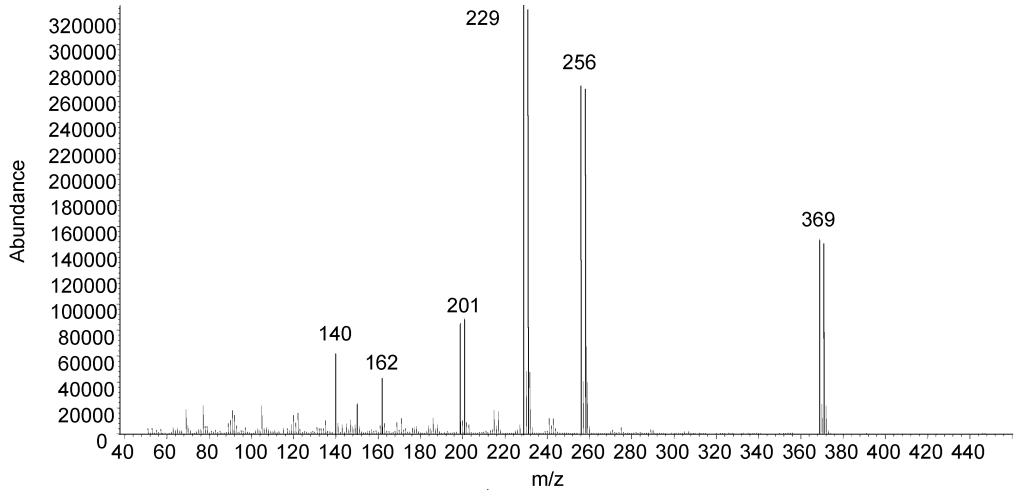


Fig. 5. The mass spectra of (±)-*N*-[2-(4-bromo-2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide.

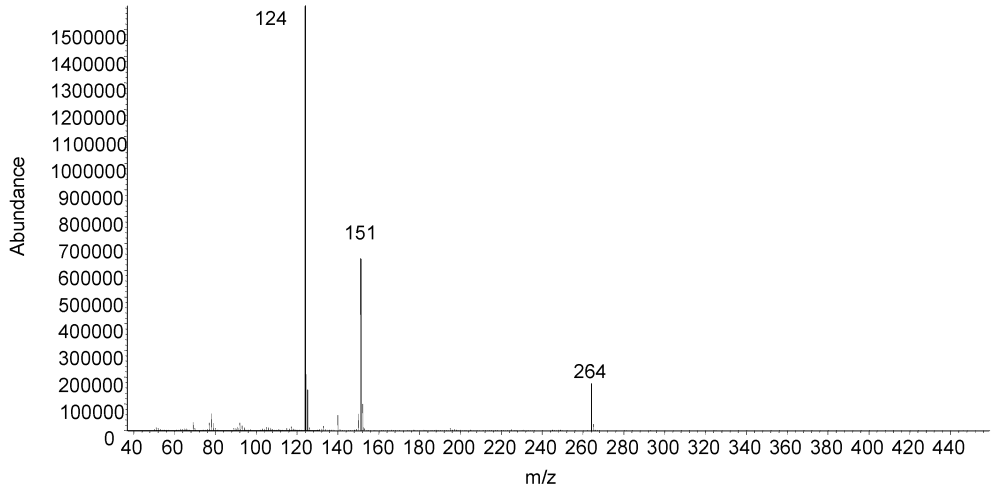


Fig. 6. The mass spectra of (±)-*N*-[2-(4-methoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_3.

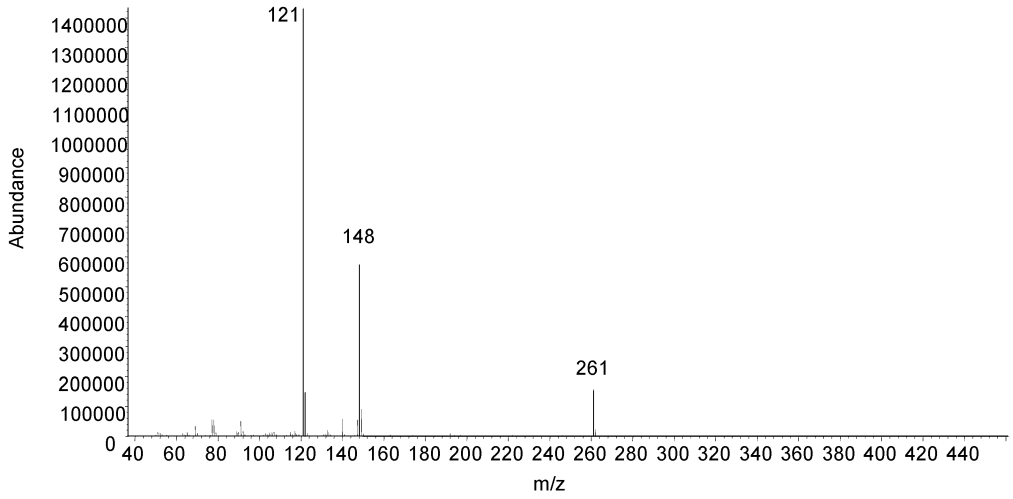
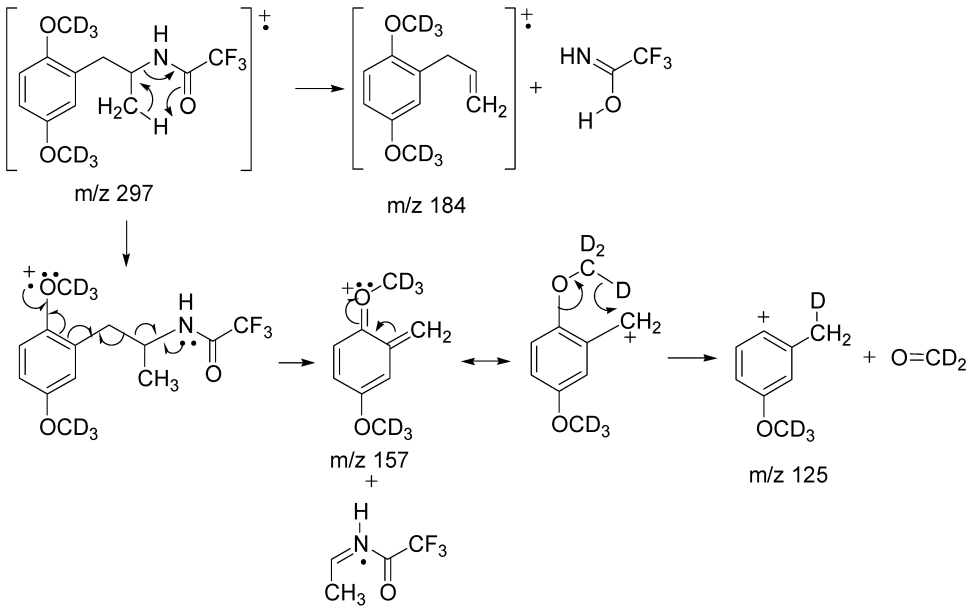


Fig. 7. The mass spectra of (±)-*N*-[2-(4-methoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide.

oxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_6 (Fig. 2) has a base peak ion at *m/z* 184. This odd electron ion was formed by a McLafferty rearrangement to eliminate a trifluoroacetamide (Scheme III). The ion *m/z* 157 was also generated by eliminating an *N*-ethylidene-2,2,2-trifluoroacetamide from the molecular ion *m/z* 297. Ion *m/z* 125 was formed from ion *m/z* 157 by the well-known specific six-center H-rearrangement of a γ-D-atom of the methoxy-d_3 (OCD_3) side chain to the benzylic part eliminating neutral formaldehyde-d_2 (CD_2O). This rearrangement was proven by comparing the mass spectrum of (±)-*N*-[2-(2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide (Fig. 2) and (±)-*N*-[2-(2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_3 (Fig. 3), because the ion *m/z* 121 corresponds to ion *m/z* 125 in *N*-[2-(2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_3, and ion *m/z* 125 has four deuterium atoms.

The EI mass spectrum of the (±)-*N*-[2-(4-bromo-2,5-

Scheme III Spectral interpretation of (±)-*N*-[2-(2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_6

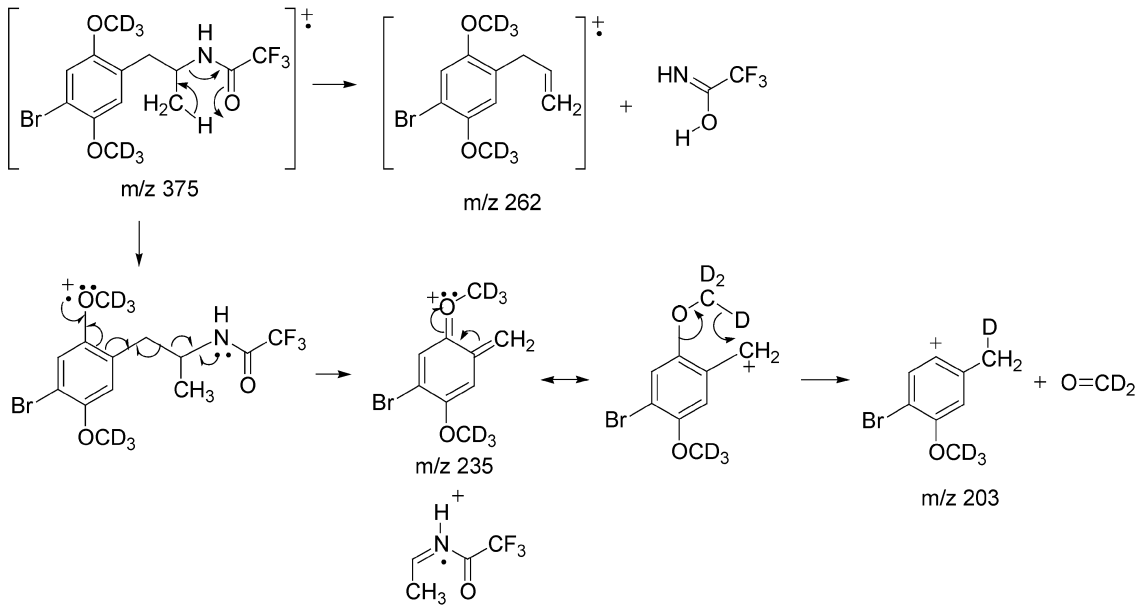


dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_6 (Fig. 4) has a base peak ion at *m/z* 235, which was formed by eliminating an *N*-ethylidene-2,2,2-trifluoroacetamide the from molecular ion *m/z* 375 (Scheme IV). Ion *m/z* 262 was formed from ion *m/z* 375 by McLafferty rearrangement, eliminating trifluoroacetamide. Ion *m/z* 203 was formed from ion *m/z* 235 by the well-known specific six-center H-rearrangement of a γ-D-atom on the methoxy-d_3 (OCD_3) side chain to the benzylic part, eliminating neutral formaldehyde-d_2 (CD_2O). This rearrangement was proven by comparing the mass spectra of Fig. 4 and Fig. 5. DOB-d_6 contains a bromine, and ions *m/z* 375, 262, 235 and 203, which always have corresponding isotopic ions *m/z* 377, 264, 237 and 205.

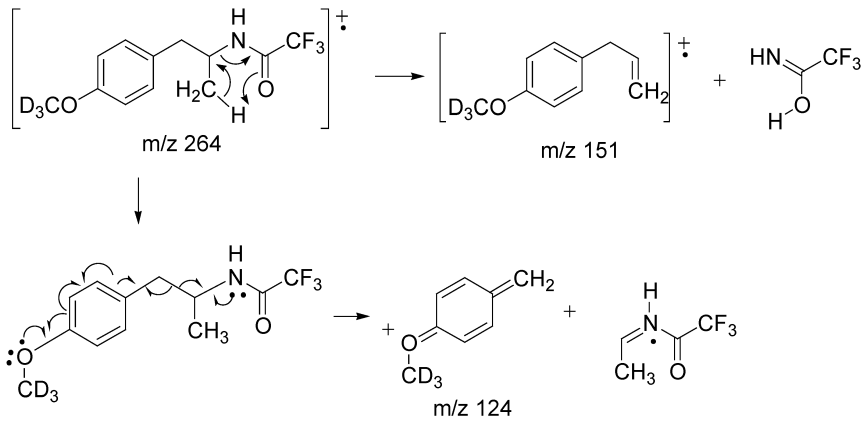
The EI mass spectrum of the (±)-*N*-[2-(4-methoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_3 (Fig. 6) has a base peak ion at *m/z* 124, which was formed by eliminating an *N*-ethylidene-2,2,2-trifluoroacetamide from molecular ion *m/z* 264 (Scheme V). Ion *m/z* 151 was formed from ion *m/z* 264 by McLafferty rearrangement to eliminate a trifluoroacetamide.

In conclusion, this study demonstrates the syntheses

Scheme IV Spectral interpretation of (±)-*N*-[2-(4-bromo-2,5-dimethoxyphenyl)-1-methylethyl]-2,2,2-trifluoroacetamide-d_6



Scheme V Spectral interpretation of (±)-*N*-[2-(4-methoxyphenyl)-1-methylethyl]-2,2,2- trifluoroacetamide



of (±)-2,5-dimethoxyamphetamine-d_6, (±)-4-bromo-2,5-dimethoxyamphetamine-d_6 and (±)-4-methoxyamphetamine-d_3. Although the retention times of GCs of three sets of labeled and unlabeled compounds vary very little (0.01 min), the quantification by MS with the selected ion monitoring (SIM) technique enhances the performance of quantitative analysis. Therefore, three deuterium-labeled compounds possess the potential to be used as the internal standard for GC-MS analysis.

EXPERIMENTAL SECTION

Methanol and ethyl acetate were obtained from Mallinckrodt (Paris, KY, USA). Trifluoroacetic anhydride (TFA) was purchased from Fluka (Buchs, Switzerland). Stock solutions of analytes and their deuterium analog (100 μg/mL) were prepared in methanol. Subsequent working solutions for calibration samples were prepared by diluting stock solutions with methanol.

A Hewlett Packard 6890 gas chromatograph, coupled to a Hewlett Packard 5973 quadrupole mass spectrometer under EI conditions, was employed. Injection was performed in splitless mode. The flow rate of the carrier gas (He) was 0.6 mL/min. An HP-5MS column (12.5 m × 0.20 mm ID, 0.33 μm film thickness; Agilent Technologies, Palo Alto, CA, USA) was employed. The injection port temperature was maintained at 250 °C. The GC oven temperature program started at 70 °C, at which temperature was maintained for 0.5 min, before it was increased at 30 °C/min to 250 °C, at which it was maintained there for 0.5 min. 1 μL of the sample was injected for GC/MS analysis in full scan monitoring mode. The total analytic time was 12 min per sample with a solvent delay of 3.0 min. The transfer line temperature and MS source temperature were 280 °C and 230 °C, respectively. The electron energy of MS was set to 70 eV. Full scan mass spectra of analytes and their deuterium analogs were collected in the range *m/z* 50-450 at a scan rate of 3.62 scan/sec.

To a clean 12-mL screw-cap glass tube was added analyte and 500 ng of deuterium analog. The mixture was evaporated to dryness under a stream of nitrogen gas at 50-60 °C. The dried extract was dissolved in 50 μL of ethyl acetate and derivatized with 50 μL of trifluoroacetic anhydride for 30 min at 60 °C. Samples were then cooled to room temperature, evaporated to dryness, and reconstituted by adding 50 μL of ethyl acetate. 1 μL was injected for GC/MS analysis.

General Chemical Procedures

^{1}H NMR spectra were acquired at 300 MHz (indicated in each case), and ^{13}C NMR were acquired at 75.5 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were obtained on a Micromass Platform II mass spectrometer at a 70 eV. High resolution mass spectra (HRMS) were obtained on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded on an ATI Mattson spectrometer. All reactions were performed in anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone in argon. Toluene, acetonitrile, dichloromethane, and hexane were distilled from calcium hydride. All air sensitive reactions were performed in dry glassware under nitrogen using a standard glovebox. Flash column chromatography was performed using MN silica gel 60 (70-230 mesh) which was purchased from Macherey-Nagel.

1,4-Dimethoxybenzene-d_6 (2)

Adequate amounts of potassium hydroxide pellets (4.30 g, 77.0 mmol) were ground to powder; tetrabutylammonium bromide (0.39 g, 1.2 mmol) and hydroquinone (3.40 g, 30.0 mmol) were then added and blended in a nitrogen atmosphere at room temperature.[38-40] Methyl iodide-d_3 (5.6 mL, 93.0 mmol) was then added and the mixture was heated in an oil bath for 3 days at 40-45 °C. The crude mixture was then transferred to a separating funnel with water and diethyl ether and extracted using diethyl ether. The extracts were dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue, which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate-hexane (1:19) as the mobile phase producing a white crystal **2** (4.22 g, 29.0 mmol). Yield: 98%. mp: 56-57 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.90 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.7, 114.6, 55.2-54.6 (m). IR (KBr, thin film): 3164, 3106, 3061, 3044, 2505, 2217, 2065, 1943, 1867 cm^{-1}.

2,5-Dimethoxybenzaldehyde-d_6 (3)

To a solution of **2** (3.50 g, 25.0 mmol) in dry dichloromethane (478 mL) cooling in an ice bath was added titanium tetrachloride (5.0 mL, 46.0 mmol), and dichloromethoxymethane ($CHCl_2OCH_3$) (4.2 mL, 46.5 mmol) under argon atmosphere.[41-46] The dark red reaction solution was

stirred at room temperature for 15 min until the starting material was completely consumed, by monitoring with TLC. The reaction was quenched by adding 185 mL of water, and the dichloromethane layer was washed with 140 mL of water and then dried over anhydrous magnesium sulfate. The solution was filtered, and the filtrate was concentrated by rotary vacuum evaporation. The residue was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate-hexane (1:39) as the mobile phase producing a white crystal **3** (3.15 g, 18.3 mmol). Yield: 73%. mp: 51 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.48 (s, 1H), 7.33 (d, J = 3.2 Hz, 1H), 7.15 (dd, J = 9.1, 3.3 Hz, 1H), 6.95 (d, J = 9.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 189.5, 156.7, 153.5, 124.9, 123.4, 113.3, 110.4, 55.6-54.7 (m). IR (KBr, thin film): 3098, 3052, 2873, 2231, 2070, 1674, 1616, 1495, 1432, 1401, 1293, 1221 cm^{-1}. MS-FAB (*m/z*): 173 (M^+ + 1, 100). HRMS-FAB (*m/z*): [M^+] calcd for $C_9H_4D_6O_3$, 172.1004; found 172.1002.

1,4-Dimethoxy-2-(2-nitropropenyl)benzene-*d*$_6$ (4)

A solution of 2,5-dimethoxybenzaldehyde-*d*$_6$ (**3**) (3.00 g, 18.0 mmol) in glacial acetic acid (15.5 mL) was treated with nitroethane (2.17 g, 29.0 mmol) and anhydrous ammonium acetate (1.39 g, 18.0 mmol).[5-a] This mixture was heated in a steam bath for 3 h and then the excess reagent and solvent was removed under vacuum. The residue was suspended in water and extracted with dichloromethane. The extracts were dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue, which was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate-hexane (1:39) as the mobile phase producing compound **4** (3.53 g, 15.4 mmol). Yield: 86%. mp: 77-78 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.23 (s, 1H), 6.69 (q, J = 3.0 Hz, 1H), 6.87 (s, 1H), 6.85 (d, J = 2.9 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.1, 152.7, 147.7, 130.1, 122.5, 115.7, 115.4, 111.7, 55.4-54.6 (m), 14.11. IR (KBr, thin film): 3070, 2923, 2854, 2356, 2248, 2225, 2071, 1646, 1496, 1427, 1295, 1268, 1238 cm^{-1}. MS-FAB (*m/z*): 230 (M^++1, 3), 214 (9), 184 (100), 115 (1). HRMS-FAB (*m/z*): $[M]^+$ calcd for $C_{11}H_7D_6NO_4$, 229.1251; found 229.1221.

(±)-1-(2,5-Dimethoxyphenyl)-2-propaneamine-*d*$_6$ (5)

A solution of (±)-1-(2,5-dimethoxyphenyl)-2-nitropropene-*d*$_6$ (**4**) (1.75 g, 7.8 mmol) in anhydrous diethyl ether (53.0 mL) was added slowly to a well-stirred suspension mixture of lithium aluminum hydride (1.19 g, 31.4 mmol) in anhydrous diethyl ether (10.8 mL). The mixture was then brought up to a reflux and maintained there for 20 h, cooled with an external ice bath, and the excess hydride was destroyed by the cautious addition of water. The quenched mixture was filtered through celite, washed with diethyl ether, and the filtrate was diluted with water to a total volume of 54 mL. Then potassium sodium tartrate (3.30 g, 113.0 mmol) was added, and sufficient aqueous sodium hydroxide added to bring the pH above 9. The two phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue, which was dissolved in dry diethyl ether, and saturated with hydrogen chloride. The formed crystals of 2,5-dimethoxyamphetamine hydrochloride-*d*$_6$ (2,5-DMA-*d*$_6$, **5**) were collected by filtration, washed with anhydrous diethyl ether, and dried to constant weight. The hydrochloric acid salt of **5** was crystallized from ethanol/diethyl ether, and gave **5** (1.27 g, 5.48 mmol). Yield: 70%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.79-6.69 (m, 3H), 3.22-3.15 (m, 1H), 2.74-2.46 (m, 2H), 1.11 (d, J = 3.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.1, 151.7, 129.1, 117.1, 111.1, 111.0, 55.0-54.1 (m), 46.9, 43.2, 41.1, 23.4. IR (KBr, thin film): 3359, 3289, 3066, 3043, 2962, 2923, 2869, 2248, 2213, 2129, 2067, 1589, 1496, 1234, 1110, 686 cm^{-1}. MS-EI (*m/z*): 201 (6), 194 (15), 192 (50), 174 (33), 158 (100), 140 (26). HRMS-EI (*m/z*): [M^+] calcd for $C_{11}H_{11}D_6NO_2$, 201.1629; found 201.1637.

(±)-1-(4-Bromo-2,5-dimethoxyphenyl)-2-propaneamine-*d*$_6$ (6)

To a well-stirred solution of 2,5-dimethoxyamphetamine hydrochloride-*d*$_6$ (**5**) (0.38 g, 1.9 mmol) in glacial acetic acid (3 mL) was added a solution of elemental bromine (0.06 mL, 1.2 mmol) in acetic acid (0.5 mL) over 5 min. The slightly exothermic reaction was allowed to stir for 3 h, and then added to water (20 mL). The cloudy solution was washed with diethyl ether, made basic with aqueous sodium hydroxide, and extracted with dichloromethane. Evaporation of the solvent from the pooled extracts gave a pale amber oil which was dissolved in 20 mL anhydrous diethyl ether and saturated with anhydrous hydrogen chloride. The fine white crystals of (±)-2,5-dimethoxy-4-bromoamphetamine hydrochloride-*d*$_6$ (**6**), were collected by filtration, Et_2O washed, and air dried to give product **6** (0.40 g, 1.4 mmol). Yield: 74%. ^{1}H NMR (300 MHz, $CDCl_3$,

δ): 7.02 (1H), 6.72 (s, 1H), 3.21 (t, *J* = 6.9 Hz, 1H), 2.71-2.44 (m, 2H), 1.11 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 152.1, 149.7, 128.3, 115.8, 115.3, 108.9, 46.9, 41.0, 23.6. IR (KBr, thin film): 3336, 3239, 3154, 2954, 2919, 2873, 2213, 2071, 1488, 1392, 1230 cm^{-1}. MS-EI (*m/z*): 281 (8), 279 (6), 265 (4), 263 (5), 238 (99), 236 (100), 220 (13), 218 (11), 205 (10), 203 (11), 143 (10), 78 (38). HRMS-EI (*m/z*): [M$^+$] calcd for $C_{11}H_{10}D_6NO_2Br$, 279.0734; found 279.0733.

4-Methoxybenzaldehyde-*d*$_3$ (8)

Adequate amounts of potassium hydroxide pellets (0.92 g, 16.0 mmol) were ground to powder; tetrabutylammonium bromide (83 mg, 0.3 mmol) and 4-hydroxybenzaldehyde (2.00 g, 16.0 mmol) were then added and blended in a nitrogen atmosphere at room temperature.[5-a] Methyl iodide-*d*$_3$ (0.52 g, 819 mmol) was then added and the mixture was heated in an oil bath for three days at 40-45 °C. The crude mixture was then transferred to a separating funnel with water and extracted using dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue, which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate-hexane (1:39, 1:19) as the mobile phase producing compound **8** (1.02 g, 7.3 mmol). Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.88 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 190.8, 164.6, 131.9, 129.9, 114.3, 55.3-54.1 (m). IR (KBr, thin film): 3358, 3066, 2922, 2743, 2258, 2222, 2070, 1693, 1598, 1504, 1316 cm^{-1}. MS-FAB (*m/z*): 140 (M$^+$+1, 17), 138 (45), 124 (100), 105 (62), 75 (45). HRMS-FAB (*m/z*): [M+H]$^+$ calcd for $C_8H_6D_3O_2$, 140.0787; found 140.0790.

1-Methoxy-4-(2-nitropropenyl)benzene-*d*$_3$ (9)

A solution of *p*-anisaldehyde-*d*$_3$ (**8**) (0.94 g, 6.8 mmol) in glacial acetic acid (3.8 mL) was treated with nitroethane (0.97 g, 14.0 mmol) and anhydrous ammonium acetate (0.78 g, 10.1 mmol).[5-a] This mixture was refluxed for 60 min and then the excess reagent and solvent was removed under vacuum. The residue was suspended in water and extracted with dichloromethane. The extracts were dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue, which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate-hexane (1:39) as the mobile phase producing compound **9** (0.87 g, 4.4 mmol). Yield: 66%. mp: 46-47 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.07 (s, 1H), 7.41 (d, *J* = 2.9 Hz, 2H), 6.99 (d, *J* = 3.0 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 161.1, 145.6, 133.6, 131.7, 125.7, 114.8, 55.2-55.3 (m), 14.0. IR (KBr, thin film): 2221, 2069, 1643, 1598, 1513, 1494, 1307, 1267, 1176 cm^{-1}. MS-FAB (*m/z*): 197 (M$^+$+1, 48), 181 (59), 150 (27), 149 (100), 132 (50). HRMS-FAB (*m/z*): [M]$^+$ calcd for $C_{10}H_8D_3NO_3$, 196.0924; found 196.0925.

(±)-1-(4-Methoxyphenyl)-2-propaneamine-*d*$_3$ (10)

To a suspension of lithium aluminum hydride (0.84 g, 22.1 mmol) in anhydrous diethyl ether (30.0 mL) was added a solution of (±)-1-(4-methoxyphenyl)-2-nitropropene-*d*$_3$ (**9**) (0.87 g, 4.4 mmol) in diethyl ether (30.0 mL), and it was added at a rate that maintained a reflux. After the addition was complete, reflux was continued for 48 h. The reaction mixture was cooled, and the excess hydride was destroyed by the cautious addition of dilute sulfuric acid. The quenched mixture was filtered through celite and washed with diethyl ether. The organic phase was separated and extracted with additional aqueous sulfuric acid. A solution of potassium sodium tartrate (21.00 g, 74.4 mmol) in water (18 mL) was added, and the pH brought to > 9 with 25% sodium hydroxide. This aqueous phase was extracted using dichloromethane; after removal of the solvent, it provided a clear amber oil **10**. Compound **10** was dissolved in 10 mL 2-propanol, saturated with hydrogen chloride, and then diluted with 10 mL anhydrous diethyl ether. After standing overnight, white crystals of 4-methoxyamphetamine hydrochloride-*d*$_3$ (**10**.HCl) were obtained; after filtering, diethyl ether washing and drying gave product **10**.HCl (0.57 g, 2.8 mmol). Yield: 63%. ^{1}H NMR (300 MHz, D_2O, δ): 7.15 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.52-3.41 (m, 1H), 2.83-2.70 (m, 2H), 1.18 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, D_2O, δ): 157.9, 130.6, 128.5, 114.3, 55.1-53.9 (m), 49.3, 49.2, 39.2, 17.4. IR (KBr, thin film): 2942, 2802, 2748, 2603, 2213, 2190, 2065, 1513, 1261, 1114, 993 cm^{-1}. MS-FAB (*m/z*): 169 (M$^+$-Cl, 100), 152 (92), 151 (8), 150 (4). HRMS-FAB (*m/z*): [M−Cl]$^+$ calcd for $C_{10}H_{13}D_3NO$, 169.1416; found 169.1417.

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